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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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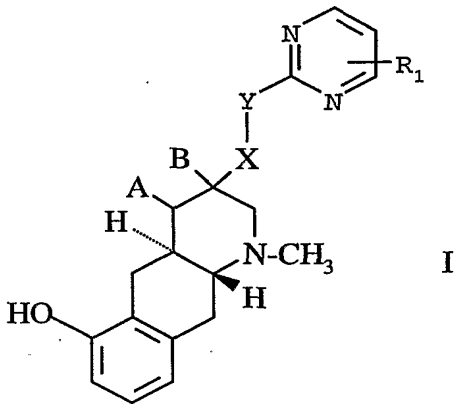
(54) Title: BENZO [G] QUINOLINE DERIVATIVES FOR TREATING GLAUCOMA AND MYOPIA

(57) Abstract: The invention provides a compound of formula I wherein A, B, X, Y and R_1 are as defined in the description, and a process for preparing them. The compounds of formula I are useful as pharmaceutical agents for the treatment of glaucoma and myopia.

BENZO'G!QUINOLINE DERIVATIVES FOR TREATING GLAUCOMA AND MYOPIA

The present invention relates to novel benzo[g]quinoline derivatives, their preparation, their use as pharmaceuticals and pharmaceutical compositions containing them.

More particularly the present invention provides a compound of formula I



I

wherein

A and B are each H or form together an additional bond,

X is CH_2 or CO,

Y is O, S, NR_2 [R_2 being H or (C_{1-4})alkyl], CH_2 or O-CH_2, and

R_1 is H or (C_{1-4})alkyl

in free base or acid addition salt form.

The above-defined alkyl groups preferably represent methyl.

When A and B are each H, the X-Y-pyrimidine substituent preferably presents the configuration 3R.

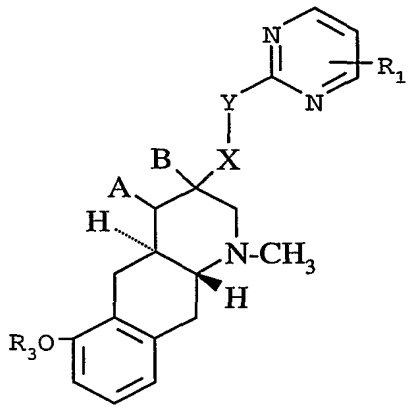
X is preferably CH_2.

Y is preferably O or S, even more preferably S.

R_1 is preferably methyl, more preferably methyl in position 4 of the addressed pyrimidine.

In a preferred embodiment A and B each represents H, X is CH_2, Y represents S and R_1 is methyl.

In a further aspect the invention provides a process for the production of the compounds of formula I and their acid addition salts, whereby in a compound of formula II



II

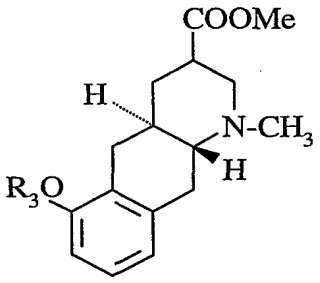
wherein A, B, X, Y and R_1 are as defined above and R_3 is (C_{1-4})alkyl, the alkoxy group is converted into a hydroxy group, and the compounds of formula I thus obtained are recovered in free base or acid addition salt form.

The reaction can be effected according to known methods, e.g. using hydrobromide acid or boron tribromide. In formula II, R_3 is preferably methyl.

Working up the reaction mixtures obtained according to the above process and purification of the compounds thus obtained may be carried out in accordance to known procedures.

Acid addition salts may be produced from the free bases in known manner, and vice versa. Suitable acid addition salts for use in accordance with the present invention include for example the hydrochloride.

The starting compounds of formula II wherein A and B are each H may be produced from the corresponding compounds of formula III_a

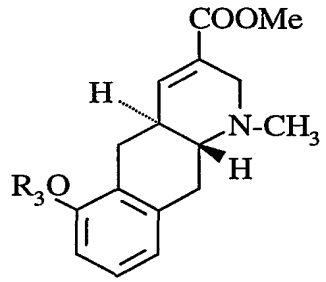


III_a

wherein R_3 is as defined above, for example as described in Example 1.

The compounds of formula III_a are known or may be produced in analogous manner to known procedures.

The starting compounds of formula II wherein A and B together form an additional bond may be produced from the corresponding compounds of formula III_b



III_b

wherein R_3 is as defined above.

The compounds of formula III_b are known or may be produced in analogous manner to known procedures.

The compounds of formula I and their physiologically acceptable acid addition salts, referred to hereinafter as agents of the invention, exhibit valuable pharmacological properties in animal tests and are therefore useful as pharmaceuticals.

In particular, the agents according to the invention effect a decrease on the intraocular pressure in rabbits, at concentrations of e.g. 10 to 100 μM. Male rabbits of ca. 2.5 kg are fixed in cages leaving their heads free. The solutions with the compound to be tested are

applied to the right eye and the placebo solutions to the left eye (2 drops each, i.e. ca. 40µl). The eyes are firstly anaesthetized with a solution containing Novesine (0.4 %) and Fluorescein (0.05 %) and the ocular pressure is determined at various intervals after administration (10, 20, 30, 60, 90, 120, 180 and 240 minutes), whereby an applanation tonometer according to Goldberg is used.

The agents of the present invention, in particular the preferred agents, exhibit a surprising strong efficacy in lowering the intraocular pressure (IOP) and an excellent duration of action. Moreover, they exhibit an excellent tolerability.

The agents according to the invention are therefore in particular useful in the treatment of glaucoma and myopia. A more preferred use is glaucoma treatment, lowering of IOP.

For the above mentioned indication, the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.1 to about 10 mg/kg animal body weight. In larger mammals, for example humans , an indicated daily dosage is in the range from about 5 to about 200 mg, preferably about 10 to about 100 mg of the compound conveniently administered in divided doses up to 4 times a day or in sustained release form.

The agents of the invention may be administered in free form or in pharmaceutically acceptable salt form. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free compounds.

Accordingly the present invention provides an agent of the invention for use as a pharmaceutical, e.g. in the treatment of glaucoma and myopia.

The present invention furthermore provides a pharmaceutical composition comprising an agent of the invention in association with at least one pharmaceutically acceptable diluent or carrier. Such compositions may be formulated in conventional manner. Unit dosage forms contain, for example, from about 0.25 to about 50 mg of an agent according to the invention.

Agents according to the invention may be administered by any conventional route, for example parenterally e.g. in form of injectable solutions or suspensions, or enterally, preferably orally, e.g. in the form of tablets or capsules.

More preferably, they are applied topically to the eye in about 0.0001 to 2 %, preferably in about 0.001 to 0.5 %, and more preferably in about 0.01 to 0.1 % ophthalmological solutions.

The ophthalmic vehicle is such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye.

The pharmaceutically acceptable ophthalmic vehicle may be e.g. an ointment, vegetable oil, or an encapsulating material.

In accordance with the foregoing, the present invention also provides an agent of the invention for use as a pharmaceutical in the treatment of glaucoma and myopia.

Moreover the present invention provides the use of an agent of the invention, for the manufacture of a medicament for the treatment of glaucoma and myopia.

In still a further aspect the present invention provides a method for the treatment of glaucoma and myopia in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of an agent of the invention.

The present invention relates also to any compound disclosed in the working examples. It further relates to any independent and/or dependant claims disclosed infra.

The following examples illustrate the invention. The temperatures are given in degrees Celsius and are uncorrected.

Example 1

[3R,4aR,10aR]-1-methyl-3β-{4-methyl-1,3-pyrimidin-2yl}thiomethyl-6-hydroxy-1,2,3,4,4aα,5,10,10aβ-octahydrobenzo[g]quinoline

a) [3R,4aR,10aR]-1-methyl-3β-hydroxymethyl-6-methoxy-1,2,3,4, 4aα,5,10, 10aβ-octahydrobenzo[g]quinoline

To a solution of 5.78g (20 mM) [3R,4aR,10aR]-1-methyl-3β-methoxycarbonyl-6-methoxy-1,2,3,4,4aα,5,10,10aβ-octahydrobenzo[g]quinoline in 100 ml toluene, a solution of 12 ml SDBA (70 % in toluene, 42 mM) is added in drops under argon at room temperature within one hour. Then 10 ml NaOH (30 %) are added in drops to the ice cooled reaction mixture. The precipitated crystals are filtered off, washed with water and toluene and dried. The resulting title compound has a m.p. of 148°; $[\alpha]^{20}_D$ = -120° (c = 0.425 in ethanol).

b) [3R,4aR,10aR]-1-methyl-3β-mesyloxymethyl-6-methoxy-1,2,3,4,4aα,5,10, 10aβ-octahydrobenzo[g]quinoline

12 ml (153 mM) methanesulfochloride are added in drops to a solution of 20 g (76.5 mM) of the compound obtained under a) in 150 ml pyridine at room temperature. The temperature is kept below 45° by ice cooling. After stirring for 2 hours at room temperature, the solution is adjusted to pH 7-8 with saturated $KHCO_3$ solution at 0° and extracted with ethylacetate. After drying over Na_2SO_4, filtering and concentrating by evaporation, the title compound is obtained as beige crystals and directly used for the next step.

c) [3R,4aR,10aR]-1-methyl-3β-{4-methyl-1,3-pyrimidin-2yl }thiomethyl-6-methoxy-1,2,3,4,4aα,5,10,10aβ-octahydrobenzo[g]quinoline

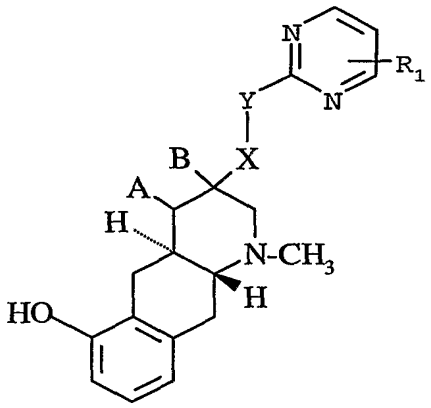
A solution of 6 g (17.7 mM) of the compound obtained under b) and 3.4 g (27 mM) 2-mercapto-4-methyl-1,3-pyrimidin in 60 ml dimethylformamide is mixed with 6 ml 2N NaOH and stirred at 65° for 18 hours. The so obtained suspension is concentrated by evaporation. The crude product crystallises. The suspension is cooled to 5-10°, washed with ethylacetate and dried. Chromatography on silicagel with ethylacetate containing 10 % ethanol and 0.01 % NH_3 yields the title compound as beige crystals.

d) [3R,4aR,10aR]-1-methyl-3β-{4-methyl-1,3-pyrimidin-2yl}thiomethyl-6-hydroxy-1,2,3,4,4aα,5,10,10aβ-octahydrobenzo[g]quinoline

To a solution of 4.06 g (11 mM) of the product obtained under c) in 250 ml methylenechloride, 40 ml of boron tribromide (1 M in methylenechloride) are slowly added in drops at a temperature of -40°. The suspension is stirred for 2 hours at room temperature, neutralized with NH_3 and extracted with a mixture of 150 ml methylenechloride and 100 ml isopropanol. After drying over Na_2SO_4, filtering and concentration by evaporation, the title compound crystallises. The corresponding hydrochloride crystallises from methanol/ethanol 1:1 during evaporation. M.p. 254°; $[\alpha]^{20}_D$ = -90° (c = 0.540 in ethanol/water 1:1). $C_{20}H_{25}N_3OS$ (HCl), MW=391.97.

CLAIMS:

1. A compound of formula I



I

wherein

A and B are each H or form together an additional bond,

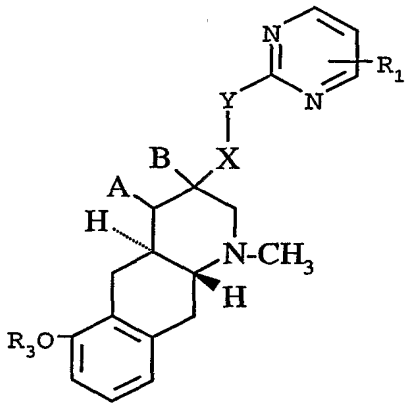
X is CH_2 or CO,

Y is O, S, NR_2 [R_2 being H or (C_{1-4})alkyl], CH_2 or O-CH_2, and

R_1 is H or (C_{1-4})alkyl

in free base or acid addition salt form.

2. A process for the preparation of a compound of formula I as defined in claim 1, or a salt thereof, which includes the step of converting, in a compound of formula II



II

wherein A, B, X, Y and R_1 are as defined in claim 1 and R_3 is (C_{1-4})alkyl, the alkoxy group into a hydroxy group and recovering the thus obtained compound of formula I in free base or acid addition salt form.

3. A compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.

4. A compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for use in the treatment of glaucoma and myopia.

5. A pharmaceutical composition comprising a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

6. The use of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, as a pharmaceutical for the treatment of glaucoma and myopia.

7. The use of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the treatment of glaucoma and myopia.

8. A method for the treatment of glaucoma and myopia in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form.

INTERNATIONAL SEARCH REPORT

Int ial Application No
P.. .? 02/07594

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 A61K31/505 A61P27/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 01444 A (NOVARTIS A.-G., SWITZ.;GULL, PETER; MARKSTEIN, RUDOLF; SEILER, MAX PET) 15 January 1998 (1998-01-15) the whole document	1-7
Y	EP 0 659 430 A (SANDOZ LTD., SWITZ.;SANDOZ-PATENT-G.M.B.H.; SANDOZ ERFINDUNGEN VERWALT) 28 June 1995 (1995-06-28) the whole document	1-7
Y	EP 0 512 952 A (SANDOZ-PATENT-G.M.B.H., GERMANY) 11 November 1992 (1992-11-11) the whole document	1-7

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 October 2002	28/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Schuemacher, A

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INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/EP 02/07594

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 03054 A (SANDOZ LTD., SWITZ.;SANDOZ-PATENT-GMBH; SANDOZ-ERFINDUNGEN VERWALTUNGS) 30 January 1997 (1997-01-30) table p.10, Ex.7	1

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/EP 02/07594

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 8 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

In nal Application No
PC.,EP 02/07594

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Int I Application No
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